



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/135, 31/165, 45/06	A1	(11) International Publication Number: WO 99/52522 (43) International Publication Date: 21 October 1999 (21.10.99)
(21) International Application Number: PCT/GB99/01153 (22) International Filing Date: 15 April 1999 (15.04.99) (30) Priority Data: 9808015.3 15 April 1998 (15.04.98) GB (71) Applicant (for all designated States except US): KING'S COLLEGE, LONDON UNIVERSITY [GB/GB]; Strand, London WC2R 2LS (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): SMITH, Kenneth, John [GB/GB]; U.M.D.S., Guy's Hospital Campus, London Bridge, London SE1 9RT (GB). KAPOOR, Raju [GB/GB]; U.M.D.S., Guy's Hospital Campus, London Bridge, London SE1 9RT (GB). (74) Agents: POWELL, Stephen, David et al.; Williams, Powell & Associates, 4 St. Paul's Churchyard, London EC4M 8AY (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PROTECTION OF THE NERVOUS SYSTEM USING SODIUM CHANNEL BLOCKERS (57) Abstract A sodium channel blocking agent is used for the treatment of an inflammatory neurological disorder of the central or peripheral nervous system especially for preventing axonal or neuronal damage. The blocking agent is administered orally or systemically, e.g. by the oral, intravenous or intramuscular route. The blocking agent may be lignocaine or mexiletine, the dosage used being in the range 100-1000 mg/day. A nitric oxide synthase inhibitor is also administered, to reduce endogenous nitric oxide production.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PROTECTION OF THE NERVOUS SYSTEM USING SODIUM CHANNEL BLOCKERS

This invention relates to the treatment of neurological disorders associated with inflammation within the central or peripheral nervous system.

Inflammation within the nervous system is a major component of several neurological disorders, including multiple sclerosis, the inflammatory neuropathies (e.g. Guillain-Barré syndrome), acute spinal cord injury, and the neurological complications of AIDS. Apart from causing neural dysfunction, inflammation might directly damage neural tissue resulting in persistent neurological deficits, especially if the damage occurs in the CNS. In MS, for example, serial magnetic resonance studies indicate that progressive axonal loss is the major cause of the gradual accumulation of permanent deficit in progressive disease. Notably, pathological studies have revealed that the axons appear to be transected specifically within the MS lesions, and that the number of axons transected correlates with the severity of the inflammation. Axonal loss is also a major feature of some inflammatory demyelinating peripheral neuropathies in both patients and animals, and, unsurprisingly, it is again associated with a persistent neurological deficit. Clearly, axonal degeneration is an important cause of morbidity, but the mechanism(s) responsible for transecting the axons remains unknown. In the absence of a direct immune attack on the axons, it is assumed that they succumb to one or more of the *melée* of deleterious factors produced at inflammatory sites, such as proteases, phospholipases, cytokines and free radicals. One free radical known to be produced in raised concentrations in MS lesions is nitric oxide. Nitric oxide has a range of physiological functions at nanomolar concentrations, but at inflammatory sites it is produced at much higher concentrations following the induction of the non-constitutive form of the enzyme nitric oxide synthase (iNOS), which is capable of releasing nitric oxide in low micromolar concentrations. At such high concentrations nitric oxide can lead to a range of toxic effects, including the impairment of mitochondrial metabolism. Indeed, mitochondrial function is known to be impaired in an animal model of MS. The mitochondrial dysfunction reduces ATP synthesis and this may be expected to place at risk those cellular components with a high metabolic rate, such as axons. At present there are no known therapies to prevent neuronal, or

axonal, loss due to inflammation. There is thus no recognised therapy to prevent the progression of disability (i.e. the steady accumulation of deficit) in multiple sclerosis.

We have surmised that exposure to nitric oxide may cause irreversible axonal damage, and that axons in which metabolic activity is increased, for example by sustained impulse activity, may be particularly vulnerable to these effects. Thus, if the increased metabolic demands arising from sustained activity occur in axons with a decreased metabolic capacity due to nitric oxide, ionic homeostasis may be lost, and degeneration ensue. This hypothesis has now been proven in our experiments where axons have been exposed *in vivo* to nitric oxide at low micromolar concentrations, while concurrently inducing sustained impulse activity at physiological frequencies. The combination of nitric oxide exposure (mimicking one component of an inflammatory site) and sustained impulse activity resulted in persistent conduction block, which did not occur in control roots exposed to only one of the two insults (figure 1). Histological examination of the roots at the site of nitric oxide exposure has revealed that the persistent block is due to axonal degeneration. Thus we have reproduced in a model what we believe to be the key components responsible for axonal death in MS lesions, namely the combination of nitric oxide (in patients this is derived from the inflammation) and axonal activity (in patients this is derived from normal impulse traffic). These same factors would be expected also to be deleterious to neuronal cell bodies if inflammation occurred around the neurons. We believe that these observations are relevant to the several neurodegenerative diseases which exhibit an inflammatory component.

In separate experiments we have shown that the conduction of sustained trains of impulses can also result in degeneration at sites where axons are already damaged, such as by demyelination or early remyelination. This degeneration can occur in the absence of obvious nitric oxide, but nitric oxide makes the degeneration more widespread. In both normal axons damaged by the combination of nitric oxide and sustained impulse activity, and pathological axons damaged simply by sustained impulse activity, the morphological evidence reveals the presence of axons which have been acutely dissolved. This pathological change suggests that the axons have been killed by an excessive accumulation of intra-axonal calcium. The calcium ions activate

axoplasmic degradative enzymes, which digest the axonal architecture causing degeneration.

On the basis of these observations, we have made two deductions. First, that the damage is due to the excessive entry of cations (such as calcium and sodium ions) to the intracellular compartment, primarily as a direct or indirect consequence of the opening of sodium channels, and second, that by impairing energy metabolism nitric oxide exacerbates the problem by reducing the ability of the cell to extrude the ions via the usual energy dependent pumps. We have tested whether axons may be protected from damage by measures which reduce the entry of cations to the intracellular compartment. We have examined a model pharmacological agent, namely the local anaesthetic lignocaine, and used it at a threshold concentration such that sodium channels are only partially blocked, and conduction of impulses continues despite the presence of the drug. We have examined whether use of this agent may be effective in preventing or reducing axonal damage *in vivo* when axons are continuously stimulated at either 50 or 100 Hz in a medium containing low concentrations of nitric oxide. The concentration of nitric oxide chosen was within the range 0.5-7 μ M, since there is evidence to believe that this range is representative of the nitric oxide concentration likely to be present within MS lesions. The experimental arrangement is similar to that described in detail below.

Four sacral spinal roots of the rat were typically examined in parallel, and they were left in continuity at either end in order to maintain their normal blood supply. The roots were raised upon stimulating electrodes at their rostral end, and upon recording electrodes caudally. Between the pairs of electrodes, each root passed through a separate pool, 7mms in length, which contained either tissue culture medium (control roots) or a similar medium to which had been added lignocaine (50-300 μ M). The stimulation protocol for all roots consisted of 1 hour at 100Hz, followed by 2 hours at 50 or 100Hz in the presence of nitric oxide (0.5-5 μ M), followed by a further 2 hours in the absence of nitric oxide. Where roots were exposed to lignocaine, they either remained in contact with the drug throughout the experiment, or the lignocaine was removed 2 hours after the removal of the nitric oxide. Sometimes the lignocaine (and control) solutions were changed every 30 minutes in case there was any tendency of

the lignocaine solution to become more dilute over time, given the fact that the roots were normally perfused with blood.

We have found that lignocaine (100 μ M) protects axons from damage, such that axons exposed to the drug are more likely to be able to conduct impulses following exposure to nitric oxide than axons in control roots (figure 2). Furthermore, and importantly, the axons protected by lignocaine were found upon histological examination (at high resolution light microscopy and at electron microscopy) to be healthy in appearance, whereas the axons not protected by lignocaine showed clear evidence of axonal degeneration (i.e. watery or non-existent axoplasm). Figure 2 shows an experiment which was terminated after a 2 hour recovery period, but other experiments (not shown) have been protracted in order to extend the recovery period to 9 or more hours. Such experiments were undertaken to demonstrate 1) that the conduction block in unprotected roots is truly persistent, i.e. probably permanent, and 2) that the protection provided by lignocaine is not merely a temporary protection. These points were proved to be correct. It is entirely reasonable to assume that since the protected axons recover function and survive for at least 9 hours after the insult, they will survive for as long as any normal axons (i.e. for the lifetime of the animal or person). As before, histological examination of the region of the roots within the bath at the end of such long experiments revealed that the axons protected by lignocaine appeared normal, while most of the unprotected axons appeared to have undergone degeneration, as described above.

We have focused our experiments on a model sodium channel blocking agent, lignocaine. Structurally related compounds, such as mexiletine, can also be used for this purpose. Other voltage-dependent sodium channel blockers, including lamotrigine, phenytoin and carbamazepine can also be of benefit. In particular, drugs selective for persistent or non-inactivating sodium currents would also be candidates. The research stage is also facilitated by the use of drugs which have readily reversible actions, but this requirement is less important once the clinical stages have been reached, at which point it may even be disadvantageous. Ideally the drug should be lipid soluble, since this will enhance its penetration across the blood-brain barrier. However, this point is not essential since where nitric oxide is present the barrier will

already be compromised, and this may beneficially limit its localisation to inflamed areas of the CNS. Also, the drug should ideally be highly selective for sodium channels over potassium, although some activity against calcium channels could be tolerated, and it may be beneficial. Since much of the calcium which enters axons may enter via reverse operation of the sodium/calcium exchanger (consequent to a raised intra-axonal sodium ion concentration), inhibitors of this exchanger should also provide protection of axons in inflammatory areas.

In patients, sodium channel blocking agents, such as lignocaine, will typically be administered systemically. In multiple sclerosis, use of the agents is particularly indicated during relapses, or when there is other evidence of on-going inflammation within the central nervous system. It may be especially beneficial to administer sodium channel modulating drugs in conjunction with selective inhibitors of the inducible form of nitric oxide synthase: such drugs are under development and will be administered systemically. The route of administration (which may be oral, intravenous or intramuscular) and dosage (in the range 100-1000mg/day) will be determined by the particular properties of the drug chosen and will depend upon individual metabolism. The precise dosage will depend upon measurements of serum drug levels.

The present invention therefore comprises the use of a sodium channel blocking agent and/or inhibitor of nitric oxide synthase for the treatment of neurological disorders associated with the central or peripheral nervous system. The present invention also comprises a method of treatment of such disorders using the substance or substances referred to above.

The benefits include the prevention of damage to the nervous system induced by exposure to inflammation, and thereby the prevention of clinical deficit in patients.

Figure 1:

Data showing the consequences of sustained impulse conduction in the presence of the low micromolar concentration of nitric oxide suspected to be present at a site of inflammation: the inset shows the recording arrangement. The data show 4 series of

records obtained in parallel from 4 dorsal roots in a terminally anaesthetised, normal rat. The roots were left in continuity to ensure that they were in as physiological state as possible, and were raised on pairs of stimulating and recording electrodes within a mineral oil recording pool maintained at $35 \pm 0.1^\circ\text{C}$. Each root passed through a bath in which it could be exposed to different media, such as different concentrations of nitric oxide. Stimuli at twice supramaximal intensity were applied at 1 or 50Hz (as indicated) and records were obtained of the evoked compound action potentials. Each plot shows a series of individual compound action potentials obtained at 2 minute intervals by computer averaging of 64 records. The records are plotted with 3-dimensional perspective, in the order in which they were obtained, with the earliest records displayed towards the front of the plot. Each plot represents about 5-6 hours of recording time. After a control period of approximately 1 hour to ensure that the preparation was stable, the medium in the bath was changed from tissue culture medium to one releasing a sustained concentration of nitric oxide ($5\mu\text{M}$, using the nitric oxide donor DETA NONOate). After 2 hours exposure, the nitric oxide solution was removed, and the root washed and then maintained in tissue culture medium for the duration of the experiment. Notice: 1) that these normal axons are capable of conducting faithfully a sustained train of impulses at 50Hz for several hours (top left plot), including during a 2 hour period in which the medium in the bath was substituted for a control medium of "DETA NONOate" which had been depleted of its nitric oxide content. 2) that the dorsal root axons (2nd plot) are capable of conducting quite faithfully at 1Hz for several hours, including during a 2 hour period in the presence of $5\mu\text{M}$ nitric oxide. However, 3) the combination of the two insults (50Hz and nitric oxide, 3rd plot) results in a progressive conduction block, eventually involving nearly all the axons. Upon removal of the nitric oxide solution, conduction is restored to a proportion of the axons, but these axons appear to be "doomed" since they nearly all progressively lose their ability to conduct over the ensuing few hours. The final outcome is one of persistent conduction block. A higher frequency of stimulation resulted in a more severe persistent conduction block (right plot). Histological examination of the region of the 4 roots within the bath at the end of the experiment revealed that the axons in the 1st and 2nd plots appeared normal, while most of the axons in the 2 right plots had undergone degeneration since they exhibited a pale and watery axoplasm with few, if any, axoplasmic organelles.

Figure 2:

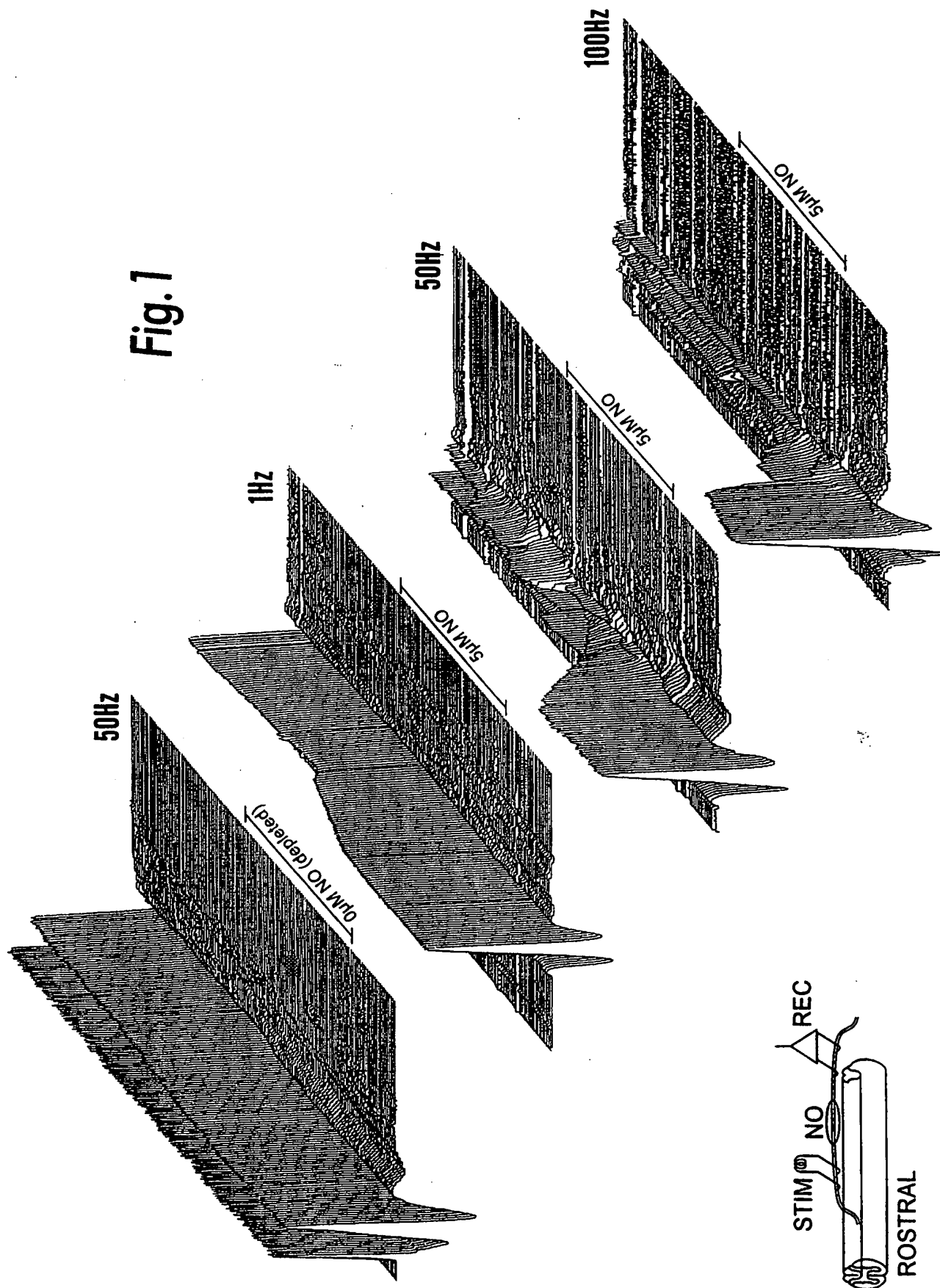
Data showing the protection of axons from degeneration by treatment with a low concentration of a sodium channel blocking agent. Notice that at this low concentration of lignocaine the axons continue to conduct entirely successfully - the concentration is way below that used by dentists to generate a nerve block. The data show 2 series of records obtained in parallel from 2 dorsal roots in a terminally anaesthetised, normal rat. The roots were prepared as described for figure 1, and the data obtained using a similar protocol, with the records obtained 2 minutes apart. The root on the left shows the same consequences of exposure to sustained activity and nitric oxide as were illustrated in figure 1. However, although the root on the right also experienced sustained activity and exposure to nitric oxide, it was protected by the inclusion in the medium of 100µM lignocaine. Notice that all, or nearly all, of the axons regain the ability to conduct. Histological examination of the region of the roots within the bath at the end of the experiment revealed that the axons protected by lignocaine appeared normal, while most of the unprotected axons had undergone degeneration, as described above.

CLAIMS

- 1) The use of a sodium channel blocking agent for the treatment of an inflammatory neurological disorder of the central or peripheral nervous system.
- 2) The use according to claim 1, for preventing axonal or neuronal damage.
- 3) A method of treating or preventing neurological disease which comprises administering a sodium channel blocking agent to a patient in need thereof.
- 4) A method according to claim 3, in which the blocking agent is administered orally or systemically, e.g. by the oral, intravenous or intramuscular route.
- 5) A method according to claim 3 or 4, in which the blocking agent is lignocaine or mexiletine.
- 6) A method according to claim 5, in which the dosage used is in the range 100-1000mg/day.
- 7) A method according to any of claims 3 to 6, in which a nitric oxide synthase inhibitor is also administered, to reduce endogenous nitric oxide production.

1/2

Fig. 1



2/2

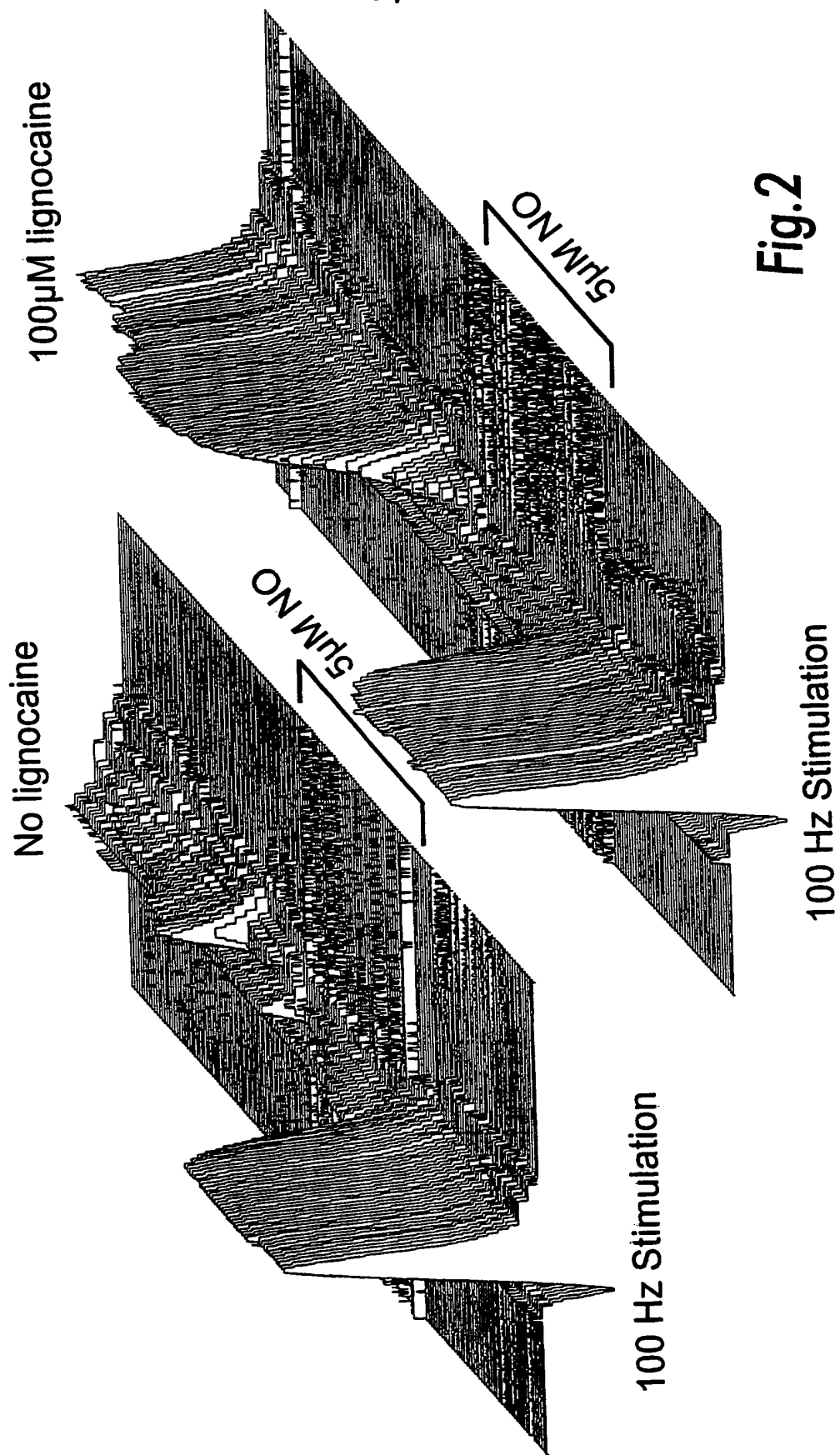


Fig.2

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01153

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/135 A61K31/165 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 27169 A (HOFFMANN LA ROCHE) 31 July 1997 (1997-07-31) page 4, line 30 - page 5, line 10 ---	1-4
X	US 5 709 869 A (HIND HARRY) 20 January 1998 (1998-01-20) claims ---	1-3,5,6
X	FR 2 702 151 A (RHONE POULENC RORER SA) 9 September 1994 (1994-09-09) claims ---	1-4
X	FR 2 702 149 A (RHONE POULENC RORER SA) 9 September 1994 (1994-09-09) claims ---	1-4

	---/---	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

23 July 1999

Date of mailing of the international search report

04/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seegert, K

INTERNATIONAL SEARCH REPORT

Ir. .ational Application No

PCT/GB 99/01153

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 13298 A (RHONE POULENC RORER SA ;DOBLE ADAM (FR); LOUVEL ERIK (FR); PRATT J) 23 June 1994 (1994-06-23) claims ---	1-4
X	WO 94 13296 A (RHONE POULENC RORER SA ;DOBLE ADAM (FR); LOUVEL ERIK (FR); PRATT J) 23 June 1994 (1994-06-23) claims ---	1-4
P,X	EP 0 869 119 A (HOFFMANN LA ROCHE) 7 October 1998 (1998-10-07) page 4, line 29 - line 39; claims ---	1-4
P,X	WO 98 32432 A (CELGENE CORP) 30 July 1998 (1998-07-30) page 1; claims ---	1-6
X	DARRELL L.T. ET AL: "Neuropathic pain can be releived by drugs that are use-dependent sodium channel blockres: lidocaine, carbamazepine, mexiletine" NESTHESIOLOGY,1991, pages 949-951, XP002913453 "Discussion" page 950 ---	1-6
X	ACKERMAN W E ET AL: "THE MANAGEMENT OF ORAL MEXILETINE AND INTRAVENOUS LIDOCAINE TO TREAT CHRONIC PAINFUL SYMMETRICAL DISTAL DISBETIC NEUROPATHY" JOURNAL OF THE KENTUCKY MEDICAL ASSOCIATION, vol. 89, October 1991 (1991-10). page 500/501 XP002913455 abstract ---	1-6
X	XU X -J ET AL: "SYSTEMIC MEXILETINE RELIEVES CHRONIC ALLODYNIALIKE SYMPTOMS IN RATS WITH ISCHEMIC SPINAL CORD INJURY" ANESTHESIA AND ANALGESIA, vol. 74, 1992, pages 649-652, XP002913451 abstract ---	1-6
X	C P TAYLOR ET AL: "TRENDS IN PHARMACOLOGICAL SCIENCES" TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 16, 1 September 1995 (1995-09-01), pages 309-316, XP002090490 page 312 - page 315 --- -/--	1-6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01153

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	OKADA S ET AL: "Two cases of multiple sclerosis with painful tonic seizures and dysesthesia ameliorated by the administration of mexiletine." JAPANESE JOURNAL OF MEDICINE, (1991 JUL-AUG) 30 (4) 373-5. JOURNAL CODE: KNY. ISSN: 0021-5120., vol. 30, no. 4, 1991, pages 373-375, XP002109033 Japan abstract	1-6
X,P	SAKURAI M. ET AL: "Positive symptoms in multiple sclerosis: Their treatment with sodium channel blockers, lidocaine and mexiletine." JOURNAL OF THE NEUROLOGICAL SCIENCES, (15 JAN 1999) 162/2 (162-168). REFS: 27 ISSN: 0022-510X CODEN: JNSCAG, vol. 162, no. 2, 15 January 1999 (1999-01-15), pages 162-168, XP002109034 Netherlands abstract	1-6
Y	DOUGLAS, S. M. (1) ET AL: "Sodium channel blockers protect against traumatic neuronal injury in the adult rat spinal cord." SOCIETY FOR NEUROSCIENCE ABSTRACTS, (1996) VOL. 22, NO. 1-3, PP. 230. MEETING INFO.: 26TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE WASHINGTON, D.C., USA NOVEMBER 16-21, 1996 ISSN: 0190-5295., vol. 22, no. 1-3, 1996, page 230 XP002109035 abstract	1-7
Y	WO 96 18617 A (MERCK & CO INC ;GUTHIKONDA RAVINDRA K (US); HAGMANN WILLIAM K (US)) 20 June 1996 (1996-06-20) page 5, line 15 - page 6, line 11	1-7
Y	US 5 246 970 A (WILLIAMSON JOSEPH R ET AL) 21 September 1993 (1993-09-21) claims	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9727169 A	31-07-1997	AU 1441797 A US 5688830 A	20-08-1997 18-11-1997
US 5709869 A	20-01-1998	US 5589180 A US 5601838 A US 5411738 A AT 161735 T CA 1338779 A DE 69031879 D DE 69031879 T EP 0388306 A ES 2110963 T GR 3026364 T JP 2300138 A JP 2515902 B	31-12-1996 11-02-1997 02-05-1996 15-01-1998 10-12-1996 12-02-1998 20-05-1998 19-09-1990 01-03-1998 30-06-1998 12-12-1990 10-07-1997
FR 2702151 A	09-09-1994	NONE	
FR 2702149 A	09-09-1994	NONE	
WO 9413298 A	23-06-1994	FR 2699077 A AT 164067 T AU 5653994 A AU 678795 B AU 5654094 A AU 5702094 A CA 2151601 A CA 2151603 A CA 2151604 A CZ 9501545 A CZ 9501546 A CZ 9501547 A DE 69317578 D DE 69317578 T DK 674512 T EP 0674520 A EP 0674512 A EP 0674518 A ES 2113635 T WO 9413296 A WO 9413288 A FR 2699079 A FR 2699078 A GR 3026403 T HU 71814 A HU 71839 A HU 71812 A JP 8504428 T JP 8504429 T JP 8504430 T MX 9307882 A MX 9307883 A MX 9307884 A NO 952228 A NO 952229 A NO 952230 A PL 309346 A PL 309347 A	17-06-1994 15-04-1998 04-07-1994 12-06-1997 04-07-1994 04-07-1994 23-06-1994 23-06-1994 23-06-1994 15-11-1995 15-11-1995 15-11-1995 23-04-1998 23-07-1998 25-05-1998 04-10-1995 04-10-1995 04-10-1995 01-05-1998 23-06-1994 23-06-1994 17-06-1994 17-06-1994 30-06-1998 28-02-1996 28-02-1996 28-02-1996 14-05-1996 14-05-1996 14-05-1996 30-06-1994 30-06-1994 30-06-1994 06-06-1995 06-06-1995 06-06-1995 02-10-1995 02-10-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9413298 A		PL 309348 A	02-10-1995
		SK 78595 A	08-05-1996
		SK 78695 A	08-05-1996
		SK 78795 A	08-05-1996
		US 5830907 A	03-11-1998
		ZA 9309399 A	22-08-1994
		ZA 9309400 A	19-08-1994
		ZA 9309401 A	19-08-1994
WO 9413296 A	23-06-1994	FR 2699077 A	17-06-1994
		AT 164067 T	15-04-1998
		AU 5653994 A	04-07-1994
		AU 678795 B	12-06-1997
		AU 5654094 A	04-07-1994
		AU 5702094 A	04-07-1994
		CA 2151601 A	23-06-1994
		CA 2151603 A	23-06-1994
		CA 2151604 A	23-06-1994
		CZ 9501545 A	15-11-1995
		CZ 9501546 A	15-11-1995
		CZ 9501547 A	15-11-1995
		DE 69317578 D	23-04-1998
		DE 69317578 T	23-07-1998
		DK 674512 T	25-05-1998
		EP 0674520 A	04-10-1995
		EP 0674512 A	04-10-1995
		EP 0674518 A	04-10-1995
		ES 2113635 T	01-05-1998
		WO 9413298 A	23-06-1994
		WO 9413288 A	23-06-1994
		FR 2699079 A	17-06-1994
		FR 2699078 A	17-06-1994
		GR 3026403 T	30-06-1998
		HU 71814 A	28-02-1996
		HU 71839 A	28-02-1996
		HU 71812 A	28-02-1996
		JP 8504428 T	14-05-1996
		JP 8504429 T	14-05-1996
		JP 8504430 T	14-05-1996
		MX 9307882 A	30-06-1994
		MX 9307883 A	30-06-1994
		MX 9307884 A	30-06-1994
		NO 952228 A	06-06-1995
		NO 952229 A	06-06-1995
		NO 952230 A	06-06-1995
		PL 309346 A	02-10-1995
		PL 309347 A	02-10-1995
		PL 309348 A	02-10-1995
		SK 78595 A	08-05-1996
		SK 78695 A	08-05-1996
		SK 78795 A	08-05-1996
		US 5830907 A	03-11-1998
		ZA 9309399 A	22-08-1994
		ZA 9309400 A	19-08-1994
		ZA 9309401 A	19-08-1994
EP 0869119 A	07-10-1998	AU 5937998 A	08-10-1998
		CA 2232147 A	03-10-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0869119 A		CN 1194977 A	07-10-1998
		CZ 9800988 A	14-10-1998
		HR 980174 A	30-04-1999
		HU 9800707 A	28-05-1999
		JP 10287649 A	27-10-1998
		NO 981495 A	05-10-1998
		NZ 330017 A	29-04-1999
		PL 325687 A	12-10-1998
		ZA 9802618 A	05-10-1998
WO 9832432 A	30-07-1998	AU 6242498 A	18-08-1998
WO 9618617 A	20-06-1996	AU 4515896 A	03-07-1996
US 5246970 A	21-09-1993	US 5358969 A	25-10-1994
		US 5710181 A	20-01-1998
		US 5837738 A	17-11-1998
		CA 2085399 A	17-06-1993
		EP 0547558 A	23-06-1993
		JP 5255079 A	05-10-1993
		US 5246971 A	21-09-1993

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)